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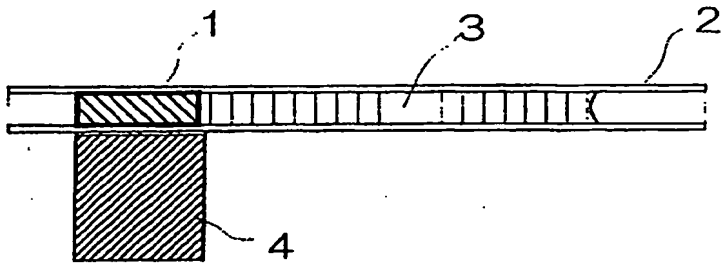
(54) Method for transporting liquid, and microreactor

(57) The present invention provides a simple liquid (3) transportation method without requiring high electric voltage or special external equipment, and a method for transporting liquid based on this transportation method. The liquid transportation method comprises a step of introducing a magnetic fluid (1) and a liquid (3) to be transported into a conduit (2) or a chamber connected thereto so that the magnetic fluid and the liquid to be transported are in contact with each other directly or indirectly via a medium, a step of moving the magnetic fluid by applying a magnetic field (4), and a step of moving above-mentioned liquid (3) to be transported by letting it follow the movement of the magnetic fluid (1).

The present invention also provides a simple transportation method of a specific amount of liquid without requiring high voltage or incorporation of specific actuator components such as valves. Using a conduit wherein at least three microchannels intersect one another and at least two of them have openings which can be opened or closed, opening and closing of the openings and liquid transportation are carried out in a controlled order, so that only a specific amount from a liquid introduced in an unspecific amount, is transported.

Fig. 1



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Description

[0001] The present invention relates to a method for transporting a liquid such as a sample or a reagent solution, which can be used for a microreactor inducing a biochemical or chemical reaction in a microregion on a substrate, as in the case of measurement using DNA chips, and to a microreactor to carry out such a liquid transportation method. The present invention also relates to a method for transporting a very small specific amount of a liquid in a case where a biochemical or chemical reaction is integrated in a microregion, which is useful for biotechnology and clinical diagnostic fields.

[0002] Various types have been developed as microreactors which are called microscale total analysis systems (μTAS), whereby a biochemical or chemical reaction is induced in a microregion on a substrate. They are expected to be very useful not only for genome analyses, postgenome analyses and medicine screening but also for clinical applications. In microreactors, a reaction chamber, a chamber to store a sample to be analyzed or a reagent solution, and a microchannel (diameter: about 1 to 1,000 μm) connecting them, are integrated in a microregion on the substrate, and it is necessary to transport a very small amount (10^{-3} to 1,000 μl) of a sample or a reagent solution in the microchannel under control.

[0003] As a conventional method for liquid transportation, a method using an electroosmosis flow pump or gas pressure, is typical. The transportation method using an electroosmosis flow pump is a method utilizing an electroosmosis flow generated in a capillary under application of high voltage, whereby the device constitution is relatively simple and therefore is easy to be integrated in a microregion. Whereas, the transportation method using gas pressure is such that a gas is introduced from outside through a gas pipe connected to the microchannel, and the liquid is transported by the pressure. In the case of using gas pressure, as it is not necessary to incorporate electric circuits such as electrodes, device manufacturing is even easier than in the case of using an electroosmosis flow pump.

[0004] However, in the case of the transportation by an electroosmosis flow pump, it is susceptible to influences of the physico-chemical characteristics (such as ionic strength or pH) of the sample or the reagent solution to be transported (liquid to be transported), whereby it is difficult to control the flow rate accurately. In the case of clinic application, it is necessary to transport a sample liquid from a living body, such as blood or urine. However, it is especially difficult to transport such a liquid having high ionic strength. Moreover, it requires a high voltage (1 to 30 kV), whereby there will be problems with respect to safety and handling efficiency.

[0005] In the case of the liquid transportation using gas pressure, it is not necessary to incorporate electric circuits such as electrodes, in addition to the microchannel, chambers, etc., as mentioned above, whereby the constitution of the microreactor can be simplified, and it has an advantage that it is not susceptible to influences of the physico-chemical characteristics of the liquid to be transported. However, on the other hand, as it requires relatively large external equipment such as compressors or syringes to feed the gas thereto, it has been difficult to miniaturize the device as an analysis system. Moreover, it has a problem that the gas volume is sensitive to the temperature, which makes fine control of the transportation difficult.

[0006] Under these circumstances, it is a first object of the present invention to provide a method for transporting a sample or a reagent solution under control, which has characteristics that it does not require relatively large external equipment and therefore is suitable for miniaturizing the device as an analysis system, excellent in safety and handling efficiency, and not susceptible to influences of the physico-chemical characteristics of the liquid to be transported; and to provide a microreactor provided with constituting elements to carry out such a liquid transportation method.

[0007] As described above, analysis systems having a biochemical or chemical reaction process integrated in a microregion, are called microscale total analysis systems (μTAS) and many trials have been reported for such systems. They are expected to be extremely effective for genome analyses, post genome analyses, medicine screening and other clinic applications. In the case of integrating a reaction process on a substrate, it is essential to transport and control a very small amount (10^{-3} to 1,000 μl) of liquid in a microchannel (1 to 1,000 μm) as an element technique. In an analytical means represented by an antigen antibody reaction or a nucleic acid amplification method, it is necessary to transport a specific amount of a sample or a reagent solution. However, it has been very difficult to introduce and transport a very small specific amount into the microchannel.

[0008] Representative techniques to transport a very small specific amount of liquid, may, for example, be a technique of using an electroosmosis pump and switching its electrodes to control the flow and thus transport a specific amount of liquid, and a technique of incorporating valves to control the amount of liquid to be transported. The electroosmosis flow pump utilizes an electroosmosis flow generated in a capillary under application of a high voltage, whereby its constitution is relatively simple, and it is easy to practically use it.

[0009] However, the electroosmosis flow pump is susceptible to influences of the physico-chemical characteristics (such as ionic strength or pH). Especially, there is a problem that it is thereby difficult to transport the liquid having high ionic strength, and thus it can hardly be applied to a sample from a living body such as blood or urine. Moreover, there have been problems with respect to safety and handling efficiency because it requires a high voltage (1 to 30 kV). Furthermore, it is not easy to integrate valves in the microregion, which is a barrier against the miniaturization. It is a

second object of the present invention to solve such problems.

[0010] To accomplish the first object, the present invention provides:

1. A method for transporting a liquid, which comprises transporting a liquid to be transported, in a conduit comprising a microchannel, or in a chamber connected to the conduit, by using a magnetic fluid as a piston.
2. The method for transporting a liquid according to Item 1, which comprises the following steps:

(1) a step of introducing the magnetic fluid and the liquid to be transported, into the conduit or the chamber connected thereto, so that the magnetic fluid and the liquid to be transported, are in contact with each other directly or indirectly via a medium,
(2) a step of moving said magnetic fluid by applying a magnetic field, and
(3) a step of moving the liquid to be transported by letting it follow the movement of the magnetic fluid.

3. The method for transporting a liquid according to Item 2, wherein said medium is either a gas or a liquid and is insoluble to said magnetic fluid and to said liquid to be transported.
4. A microreactor comprising the following constituting elements:

(1) a conduit comprising a microchannel,
(2) a chamber connected to said conduit,
(3) a magnetic fluid and a liquid to be transported, introduced into the conduit or the chamber connected thereto, so that the magnetic fluid and the liquid to be transported are in contact directly or indirectly via a medium, and
(4) a magnet to apply a magnetic field to said magnetic fluid thereby to move the magnetic fluid.

5. The microreactor according to Item 4, wherein the conduit intersects another conduit or a chamber different from the one mentioned above, so that at least two types of liquids to be transported can be mixed at the intersection.
6. The microreactor according to Item 5, wherein said at least two types of liquids to be transported, are moved by the magnetic fluid moved solely by applying a magnetic field.

To accomplish the second object, the present invention provides:

7. A method for transporting a liquid, which is a method for transporting a specific amount of an optional liquid, using a conduit wherein at least three microchannels intersect one another, and at least two of them have openings which can be opened or closed, wherein opening and closing of the openings and transportation of the liquid are carried out in a controlled order, so that a specific amount from the liquid introduced in an unspecified amount is transported.
8. The method for transporting a liquid according to Item 7, which is a method for transporting a specific amount of an optional liquid, using a conduit wherein i) first, second and third microchannels intersect one another at one intersection, ii) the first and third microchannels have first and third openings, respectively, which can be opened or closed, iii) the intersection and the second microchannel have a portion having a specific volume, which regulates the amount of the liquid filled therein, wherein a specific amount of a liquid is transported by performing a process comprising the following steps:

(1) opening the first opening, and closing the third opening,
(2) introducing an optional liquid into the first microchannel, and transporting the liquid until its front fills the specific volume portion,
(3) closing the first opening, and opening the third opening, and
(4) transporting the liquid filled in the specific volume portion of the second microchannel to the third microchannel.

9. The method for transporting a liquid according to Item 7, which is a method for transporting a specific amount of an optional liquid, using a conduit wherein, i) first, second and third microchannels intersect one another at a first intersection, and the second microchannel, a fourth microchannel and a fifth microchannel intersect one another at a second intersection, ii) the first, third, fourth and fifth microchannels have first, third, fourth and fifth openings, respectively, which can be opened or closed, iii) the first intersection, the second intersection and the second microchannel have a portion having a specific volume, which regulates the amount of the liquid filled therein, whereby a specific amount of a liquid is transported by performing a process comprising the following steps:

(1) opening the first and fifth openings, and closing the third and fourth openings,
(2) introducing an optional liquid into the first microchannel, and transporting the liquid so that the specific

volume portion is filled with the liquid,
(3) closing the first and fifth openings, and opening the third and fourth openings, and
(4) transporting the liquid filled in the specific volume portion to the third microchannel.

10. The method for transporting a liquid according to any one of Items 7 to 9, wherein the transportation of the liquid is performed by controlling the pressure of a gas or a liquid filled in the microchannels.
11. The method for transporting a liquid according to Item 10, wherein the pressure control of the gas or the liquid is performed by introducing a magnetic fluid in the microchannels, and applying a magnetic field to the magnetic fluid.

[0011] In the accompanying drawings:

Fig. 1 is a schematic diagram showing the principle of transporting a liquid by a magnetic fluid.
Fig. 2 is a schematic diagram showing a microreactor based on the method for transporting a liquid by a magnetic fluid.
Fig. 3 shows the principle of transporting a specific amount of liquid. A is a first microchannel, B is a second microchannel, C is a third microchannel, D is an intersection, E is a first opening, F is a third opening, and G is a portion having a specific volume.
Fig. 4 shows the principle of another embodiment of transporting a specific amount of liquid. A is a first microchannel, B is a second microchannel, C is a third microchannel, D is a first intersection, E is a fourth microchannel, F is a fifth microchannel, G is a second intersection, H is a first opening, I is a third opening, J is a fourth opening, K is a fifth opening, and L is a portion having a specific volume.
Figs. 5(i) to 5(v) show a pattern of microchannels formed on a polyvinyl chloride substrate. Each of 9, 10, 11, 12, 13, 14 and 15 indicates a microchannel (width: 0.5 mm, depth: 0.5 mm). Each of 16, 17, 18, 19 and 20 indicates an opening (diameter: 5 mm, depth: 2 mm). 21 is a magnet, 22 is a magnetic fluid introduced, and 23 indicates introduced 10 mM tris-HCl (pH 7.9), 0.15 M NaCl, 5% bovin serum albumin (TBS-BSA). The Table in the Figure shows open-close status of the openings in each step of the process.

[0012] As defined in the above Item 1, the present invention provides, in order to achieve the above-mentioned first object, a method for transporting a liquid, which comprises transporting a liquid to be transported, in a conduit comprising a microchannel, or in a chamber connected to the conduit, by using a magnetic fluid as a piston.
[0013] As defined in Item 2, the present invention provides the method for transporting a liquid according to Item 1, which comprises the following steps:

(1) a step of introducing the magnetic fluid and the liquid to be transported, into the conduit or the chamber connected thereto, so that the magnetic fluid and the liquid to be transported, are in contact with each other directly or indirectly via a medium,
(2) a step of moving said magnetic fluid by applying a magnetic field, and
(3) a step of moving the liquid to be transported by letting it follow the movement of the magnetic fluid.

[0014] As defined in Item 3, the present invention provides the method for transporting a liquid according to Item 2, wherein said medium is either a gas or a liquid and is insoluble to said magnetic fluid and to said liquid to be transported.
[0015] As defined in Item 4, the present invention further provides a microreactor which comprises the following constituting elements to carry out the above-mentioned method for transporting a liquid:

(1) a conduit comprising a microchannel,
(2) a chamber connected to said conduit,
(3) a magnetic fluid and a liquid to be transported, introduced into the conduit or the chamber connected thereto, so that the magnetic fluid and the liquid to be transported are in contact directly or indirectly via a medium, and
(4) a magnet to apply a magnetic field to said magnetic fluid thereby to move the magnetic fluid.

[0016] As defined in Item 5, the present invention provides the microreactor according to Item 4, wherein the conduit intersects another conduit or a chamber different from the one mentioned above, so that at least two types of liquids to be transported can be mixed at the intersection.
[0017] And as defined in Item 6, the present invention provides the microreactor according to Item 5, wherein said at least two types of liquids to be transported, are moved by the magnetic fluid moved solely by applying a magnetic field.
[0018] Now, the present invention will be described in detail.
[0019] The microchannel and chamber are structures of from 1 to 1,000 μm in width. These structures can be formed

on a desired substrate by using conventional techniques such as photolithography. Further, in the present invention, such a microchannel or chamber can be a capillary tube such as a glass capillary. Such a microchannel can be connected to another microchannel or chamber.

[0020] The magnetic fluid used in the present invention is one having magnetic fine particles, preferably strong ferromagnetic fine particles, stably dispersed in an optional liquid, for which there is no particular restriction including the method for dispersion. For example, one having iron oxide fine particles (Fe_3O_4, diameter: about 10 nm) dispersed by a surface active agent, may be mentioned as a preferred example of the magnetic fluid. In the present invention, a commercial magnetic fluid such as APG832, EXP96009 or EXP96008 (trade name, each manufactured by Ferrotec Corp.) can also be used.

[0021] The present invention is such that a magnetic fluid is used as a piston to transport a liquid to be transported, in the conduit comprising a microchannel, and in a chamber connected to the conduit. The liquid to be transported may, for example, be a sample to be analyzed in a microreactor, a reagent solution containing a component reactive with the sample, or a buffer solution to maintain the pH of the sample and/or the reagent solution to be constant. Here, the reagent solution means one containing a component to cause a specific reaction, such as an antigen or antibody component to cause an immunologically singular binding reaction, an oligonucleotide component to cause a singular binding reaction of a nucleic acid, a component to cause a nucleic acid amplification reaction, an enzyme component to cause an enzymatic reaction, or a mixture of these components. Further, it may also be a marker component capable of generating a signal to identify the occurrence of such a reaction. Examples of such a marker component, may be, antibodies, antigens, receptors or oligonucleotides, which are combined with pigments, fluorescent substances, luminous substances, enzymes or the like.

[0022] A specific procedure of the present invention may, for example, be such that (1) a magnetic fluid and a liquid to be transported are introduced into a conduit comprising a microchannel or into a chamber connected to the conduit so that the magnetic fluid and the liquid to be transported are in contact with each other either directly or indirectly via a medium, (2) the magnetic fluid is moved by applying a magnetic field, and (3) the liquid to be transported is moved by letting it follow the movement of the magnetic fluid.

[0023] The magnetic fluid and the liquid to be transported are introduced into the microchannel or into the chamber so that they are in contact with each other directly or indirectly via a medium. In the case where they are introduced so that they are directly in contact each other, a magnetic fluid insoluble to the liquid to be transported is to be used. For example, in a case where a magnetic fluid soluble to the liquid to be transported is used, the magnetic fluid and the liquid to be transported may be brought in contact with each other indirectly via a medium which is insoluble to them. As such a medium, a gas, or a liquid insoluble to both of them, may, for example, be used.

[0024] The method for applying a magnetic field to the magnetic fluid is not particularly restricted, and a method of moving the magnetic field relatively by using an electromagnet or a permanent magnet may, for example, be mentioned. Here, if an electromagnet is used, magnetic array elements may, for example, be arranged along e.g. the conduit comprising a microchannel. And, by moving the magnetic fluid by applying a magnetic field, the liquid to be transported will be moved by the pressure of the magnetic fluid.

[0025] The present invention provides a microreactor based on the above-mentioned liquid transportation method. The microreactor of the present invention comprises (1) a conduit comprising a microchannel, (2) a chamber connected to the conduit, (3) a magnetic fluid and a liquid to be transported, introduced into the conduit or the chamber connected thereto, so that the magnetic fluid and the liquid to be transported are in contact with each other directly or indirectly via a medium, and (4) a magnet to apply a magnetic field to the magnetic fluid thereby to move the magnetic fluid. By making the conduit intersect another conduit or a chamber different from the chamber previously mentioned, it is possible to realize mixing with a liquid transported by another conduit or with a liquid introduced in another chamber at the intersection.

[0026] This is useful, for example, in a case where a sample to be analyzed by a microreactor is transported in an optional microchannel, and a reagent solution or the like to be mixed with the sample is transported in another microchannel, and they are mixed and reacted, and then transported to the chamber where a reactive component is fixed which captures only the complex formed by the reaction. It is, of course, possible that the liquid transportation by such another conduit and/or the liquid transportation by such another chamber can be achieved by the liquid transportation method of the present invention, that is, by the liquid transportation by the magnetic fluid moved by application of a magnetic field. Therefore, in the reactor of the present invention, it is preferred to arrange various elements selected from means to capture a specific reaction product therein, separating means such as micropost structures or comb structures, detection elements for e.g. electrochemical detection, and heaters, as the case requires.

[0027] Fig. 1 shows an example wherein a capillary tube is used as a microchannel. A magnetic fluid (1) is introduced into a capillary tube (2), and a liquid to be transported (3) is introduced so that it directly contacts the magnetic fluid (1). Subsequently, by moving a magnet (4) which is arranged at a position where it can move the magnetic fluid (1), the liquid to be transported, is moved in an optional direction. By the movement of the magnet, the liquid to be transported can be easily introduced into the capillary tube (2).

[0028] Now, the present invention will be described in further detail with reference to Examples. However, it should be understood that the present invention is by no means restricted to such specific Examples.

EXAMPLE 1 Liquid transportation by magnetic fluid

[0029] In accordance with the principle shown in Fig. 1, the confirmation of liquid transportation was performed by using various magnetic fluids, capillary tubes and liquids to be transported. The liquid transportation was possible with various combinations of the magnetic fluid, the capillary tube and the liquid to be transported, as identified in Table 1. As for the magnet, a neodium magnet (12×7×4 mm angular shape, surface magnetic flux density: 3,500 G) was used.

[0030] From the results shown in Table 1, it was confirmed that the liquid to be transported can be transported in an optional direction regardless of the material or inner diameter of the capillary tube. Especially, it was shown to be useful even for a liquid containing proteins at high concentrations, such as blood. Table 1 shows the combinations of the magnetic fluid, the capillary tube and the liquid to be transported, used. The magnetic fluids① ,② and③ in the Table are commercial magnetic fluids (APG 832, EXP96009 and EXP96008, trade names, manufactured by Ferrotec Corp.) respectively. Further, in the Table, the composition of TBS (Tris buffer saline)-5% or 10% BSA is 10 mM Tris-HCl (pH 7.9), 0.15 M NaCl, and 5% or 10% bovine serum albumin.

Table 1

Magnetic fluid (1)				Dilution	Material of capillary tube (2)	Inside diameter of capillary tube (μm)	Liquid to be transported (3)
Type	Solvent	Viscosity (mPa·s) at 27℃	Saturation magnetization (G)				
①	Poly-α-olefin	200	200	-	Glass	290	Water
②	Synthetic ester	38	209	-	Glass	940	TBS-5% BSA
②	Synthetic ester	38	209	-	Glass	470	TBS-5% BSA
②	Synthetic ester	38	209	-	Glass	290	TBS-5% BSA
②	Synthetic ester	38	209	-	Glass	290	Water
③	Synthetic ester	24	199	-	Glass	940	TBS-5% BSA
③	Synthetic ester	24	199	-	Glass	470	TBS-5% BSA
③	Synthetic ester	24	199	-	Glass	290	TBS-5% BSA
③	Synthetic ester	24	199	-	Glass	290	Water
③	Synthetic ester	24	199	4 times dilution by 1-butanol	Teflon	About 300	Water
③	Synthetic ester	24	199	4 times dilution by 1-butanol	Polyimide	200	Water
③	Synthetic ester	24	199	4 times dilution by 1-butanol	Glass	940	TBS-5% BSA
③	Synthetic ester	24	199	4 times dilution by 1-butanol	Glass	470	TBS-5% BSA
③	Synthetic ester	24	199	4 times dilution by 1-butanol	Glass	290	TBS-5% BSA
③	Synthetic ester	24	199	4 times dilution by 1-butanol	Glass	290	TBS-10% BSA
③	Synthetic ester	24	199	4 times dilution by 1-butanol	Glass	290	Water
③	Synthetic ester	24	199	4 times dilution by 1-butanol	Glass	140	TBS-10% BSA
③	Synthetic ester	24	199	4 times dilution by 1-butanol	Glass	140	Water

EXAMPLE 2 Microreactor based on liquid transportation by magnetic fluid

[0031] A microreactor as shown in Fig. 2 was prepared. Namely, a microchannel (6) (length: 100 mm, width: 0.5 mm, depth: 0.5 mm) and chambers (7) (8) (diameter: 5 mm, depth: 2 mm) were formed on a poly-vinyl chloride substrate (5). Then, a poly-vinyl chloride plate was bonded to the top of the microchannel, to obtain a microreactor opened upward only at the chambers.

[0032] The liquid to be transported (water or TBS-5% BSA) was introduced from the chamber (7) to the microchannel (6), and then, the magnetic fluid shown as ③ in Table 1 was diluted four times by 1-butanol and introduced from the chamber (7) or (8). Then, by moving the magnet disposed under the substrate, the liquid to be transported was moved to the other chamber.

[0033] As it is apparent from the foregoing description, the liquid transportation method of the present invention does not require relatively large external equipment, and can be carried out by movement of a small means such as a permanent magnet or an electromagnet. Besides, the actuator for moving the magnet, can also be miniaturized (it is unnecessary when the array is used). Thus, it can be said that the present invention is suitable for miniaturization as an analysis system. Furthermore, since fine control of the movement of the magnet is possible by an electric or mechanical means, accurate transportation of the liquid is possible.

[0034] In its second aspect, the present invention provides, in order to achieve the second object, a method for transporting a specific amount of liquid, which has solved the problems of the prior art involved in the integration of a reaction process in a microregion on a device. Namely, it provides a liquid transportation method which is not susceptible to influences of the physico-chemical characteristics of the liquid to be transported, does not require a high voltage, does not require to incorporate of actuator components such as valves, and thus is suitable for miniaturization and easy to handle. The present invention provides, as defined in the above Item 7, a method for transporting a liquid, which is a method for transporting a specific amount of an optional liquid, using a conduit wherein at least three microchannels intersect one another, and at least two of them have openings which can be opened or closed, wherein opening and closing of the openings and transportation of the liquid are carried out in a controlled order, so that a specific amount from the liquid introduced in an unspecified amount is transported.

[0035] The present invention provides, as defined in the above Item 8, the method for transporting a liquid according to Item 7, which is a method for transporting a specific amount of an optional liquid, using a conduit wherein i) first, second and third microchannels intersect one another at one intersection, ii) the first and third microchannels have first and third openings, respectively, which can be opened or closed, iii) the intersection and the second microchannel have a portion having a specific volume, which regulates the amount of the liquid filled therein, wherein a specific amount of a liquid is transported by performing a process comprising the following steps:.

(1) opening the first opening, and closing the third opening,
(2) introducing an optional liquid into the first microchannel, and transporting the liquid until its front fills the specific volume portion,
(3) closing the first opening, and opening the third opening, and
(4) transporting the liquid filled in the specific volume portion of the second microchannel to the third microchannel.

[0036] The present invention provides, as defined in the above Item 9, the method for transporting a liquid according to Item 7, which is a method for transporting a specific amount of an optional liquid, using a conduit wherein, i) first, second and third microchannels intersect one another at a first intersection, and the second microchannel, a fourth microchannel and a fifth microchannel intersect one another at a second intersection, ii) the first, third, fourth and fifth microchannels have first, third, fourth and fifth openings, respectively, which can be opened or closed, iii) the first intersection, the second intersection and the second microchannel have a portion having a specific volume, which regulates the amount of the liquid filled therein, whereby a specific amount of a liquid is transported by performing a process comprising the following steps:

(1) opening the first and fifth openings, and closing the third and fourth openings,
(2) introducing an optional liquid into the first microchannel, and transporting the liquid so that the specific volume portion is filled with the liquid,
(3) closing the first and fifth openings, and opening the third and fourth openings, and
(4) transporting the liquid filled in the specific volume portion to the third microchannel.

[0037] The present invention provides, as defined in the above Item 10, the method for transporting a liquid according to any one of Items 7 to 9, wherein the transportation of the liquid is performed by controlling the pressure of a gas or a liquid filled in the microchannels.

[0038] The present invention provides, as defined in the above Item 11, the method for transporting a liquid according

to Item 10, wherein the pressure control of the gas or the liquid is performed by introducing a magnetic fluid in the microchannels, and applying a magnetic field to the magnetic fluid.

[0039] Now, the second aspect of the present invention will be described in detail.

[0040] The microchannel in the present invention is a structure of from 1 to 1,000 μm in width. This structure can be formed on a desired substrate by using conventional techniques such as photolithography. Further, it may be a capillary tube such as a glass capillary. Such a microchannel can be connected to a chamber having an optional volume, as the case requires.

[0041] An embodiment of the second aspect of the present invention is such that, in a conduit wherein i) first (A in Fig. 3), second (B in Fig. 3), and third (C in Fig. 3) microchannels intersect one another at an intersection (D in Fig. 3), ii) the first and third microchannels have first (E in Fig. 3) and third (F in Fig. 3) openings, respectively, which can be opened or closed, iii) the intersection and the second microchannel have a portion having a specific volume (G in Fig. 3), which regulates the specific amount of the liquid filled therein, a specific amount of a liquid can be transported by performing a process comprising the following steps:

(1) The first opening is opened, and the third opening is closed.
(2) An optional liquid is introduced into the first microchannel, and the liquid is transported until its front fills the portion having a specific volume. The liquid can be a reagent for analysis and/or a sample, and its amount can be an unspecific amount as long as it is an amount sufficient for analysis. The specific volume can be appropriately set depending upon the condition of analysis method.
(3) The first opening is closed, then the third opening is opened.
(4) The liquid filled in the specific volume portion of the second microchannel is transported to the third microchannel.

[0042] The shape of the above-mentioned opening is not particularly restricted, and the opening can be located at an optional location as long as it does not hinder the transportation of the liquid. The method for opening or closing the above-mentioned opening is also not particularly restricted, and it can be performed by sliding a plate provided with an appropriate sealing means. Further, the liquid transportation of the above-mentioned process can be performed by controlling the pressure of a gas or a liquid filled in the microchannel. The method to control the pressure of the gas or the liquid is not particularly restricted, and it can be performed by introducing a magnetic fluid in the microchannel and applying a magnetic field to the magnetic fluid. The magnetic fluid is a liquid having ferromagnetic fine particles stably dispersed therein, and is not particularly restricted in terms of the ferromagnetic fine particles, the solvent and the method for dispersion. However, it is preferably one having fine particles of iron oxide (Fe_3O_4, particle diameter: about 10 nm) dispersed by a surface active agent. For example, as the magnetic fluid, a commercial product such as APG 832, EXP 96009, or EXP 86008 (manufactured by Ferrotec Corp.) can be used. The method for applying a magnetic field is not particularly restricted, and it may be a method wherein a magnetic field is relatively moved by using an electromagnet or a permanent magnet. In a case where an electromagnet is used, the method using magnetic array elements may be arranged along the conduit.

[0043] Another embodiment of the second aspect of the present invention is such that, in a conduit wherein i) first (A in Fig. 4), second (B in Fig. 4), and third (C in Fig. 4) microchannels intersect one another at a first intersection (D in Fig. 4), and the second microchannel and a fourth microchannel (E in Fig. 4) and a fifth microchannel (F in Fig. 4) intersect one another at a second intersection (G in Fig. 4), ii) the first, third, fourth and fifth microchannels have first (H in Fig. 4), third (I in Fig. 4), fourth (J in Fig. 4) and fifth (K in Fig. 4) openings, respectively, which can be opened or closed, iii) the second channel having its both ends at the first intersection and at the second intersection, has a specific volume and regulates the specific volume of the liquid filled in the specific volume portion (L in Fig. 4), a specific amount of a liquid can be transported by performing a process comprising the following steps:

(1) The first and fifth openings are opened, and the third and fourth openings are closed.
(2) An optional liquid is introduced in the first microchannel, and the liquid is transported so that the above-mentioned specific volume portion is filled with the liquid. The liquid can be a reagent for analysis and/or a sample, and its amount can be an unspecific amount so long as it is an amount sufficient for the analysis. Further, it does not matter that an excess liquid flows into the fifth microchannel.
(3) The first and the fifth openings are closed, and the third and the fourth openings are opened,
(4) The liquid filled in the above-mentioned specific volume portion is transported to the third microchannel.

[0044] Furthermore, by combining these systems, multiple liquids having specific and very small amounts can be transported and mixed. Namely, the present invention is effective as a transportation method of the specific amount of liquid, which can be used to miniaturize and integrate such analytical means as represented by an antibody antigen reaction or a nucleic acid amplification reaction on an optional substrate.

[0045] Now, the second aspect of the present invention will be described in further detail with reference to Examples. However, it should be understood that the present invention is by no means restricted to such specific Examples.

EXAMPLE 3 Specific amount transportation of two types of aqueous solutions

[0046] A microchannel pattern used is shown in Figs. 5(i) to 5(v). On a polyvinyl chloride substrate, the pattern comprising microchannels (9, 10, 11, 12, 13, 14 and 15, width: 0.5 mm, depth: 0.5 mm) and openings (16, 17, 18, 19 and 20, diameter: 5 mm, depth: 2 mm) was formed. As a magnet, a neodium magnet (21, 12×7×4 mm angular shape, surface magnetic flux density: 3,500 G) was used. Opening or closing of the openings was performed by sliding a glass plate transversely over the openings. Sealing was improved by applying a silicon grease to the glass plate.

(i) A magnetic fluid (EXP 96008, manufactured by Ferrotec Corp.) was introduced from openings 18 and 19.
(ii) Magnet 21 was moved rightward, whereby the magnetic fluid was introduced into microchannels 11 and 12. 5 μℓ of 10 mM Tris·HCl (pH 7.9), 0.15 M NaCl, 5% bovine serum albumin (hereinafter TBS-BSA) was introduced into openings 16 and 17.
(iii) Opening 20 was closed, and magnet 21 was moved leftward, whereby the TBS-BSA was introduced into each of microchannels 11 and 12 in a length of 8 mm (each specific volume portion: volume 2 μℓ).
(iv) Openings 16 and 17 were closed, and opening 20 was opened. By moving magnet 21 rightward, the respective TBS-BSA filled in the specific volume portions (volume 2 μℓ each) were transported to microchannels 13 and 14, respectively.
(v) Then, by moving magnet 21 rightward, the respective TBS-BSA were mixed in microchannel 15 and moved to opening 20. Consequently, TBS-BSA in an amount of 4 μℓ was recovered at the opening 20.

[0047] As is evident from the above result, by the method of the present invention, even though it is simple in constitution, it has been made possible to transport a very small specific amount of a liquid in a microchannel.

[0048] The entire disclosures of Japanese Patent Application No. 2001-194729 filed on June 27, 2001 and Japanese Patent Application No. 2001-237650 filed on August 6, 2001 including specifications, claims, drawings and summaries are incorporated herein by reference in their entirety.

[0049] The present invention provides a simple liquid transportation method without requiring high electric voltage or special external equipment, and a method for transporting liquid based on this transportation method. The liquid transportation method comprises a step of introducing a magnetic fluid and a liquid to be transported into a conduit or a chamber connected thereto so that the magnetic fluid and the liquid to be transported are in contact with each other directly or indirectly via a medium, a step of moving the magnetic fluid by applying a magnetic field, and a step of moving above-mentioned liquid to be transported by letting it follow the movement of the magnetic fluid.
The present invention also provides a simple transportation method of a specific amount of liquid without requiring high voltage or incorporation of specific actuator components such as valves. Using a conduit wherein at least three microchannels intersect one another and at least two of them have openings which can be opened or closed, opening and closing of the openings and liquid transportation are carried out in a controlled order, so that only a specific amount from a liquid introduced in an unspecific amount, is transported.

Claims

1. A method for transporting a liquid, which comprises transporting a liquid to be transported, in a conduit comprising a microchannel, or in a chamber connected to the conduit, by using a magnetic fluid as a piston.

2. The method for transporting a liquid according to Claim 1, which comprises the following steps:

   (1) a step of introducing the magnetic fluid and the liquid to be transported, into the conduit or the chamber connected thereto, so that the magnetic fluid and the liquid to be transported, are in contact with each other directly or indirectly via a medium,
   (2) a step of moving said magnetic fluid by applying a magnetic field, and
   (3) a step of moving the liquid to be transported by letting it follow the movement of the magnetic fluid.

3. The method for transporting a liquid according to Claim 2, wherein said medium is either a gas or a liquid and is insoluble to said magnetic fluid and to said liquid to be transported.

4. A microreactor comprising the following constituting elements:

(1) a conduit comprising a microchannel,
(2) a chamber connected to said conduit,
(3) a magnetic fluid and a liquid to be transported, introduced into the conduit or the chamber connected thereto, so that the magnetic fluid and the liquid to be transported are in contact directly or indirectly via a medium, and
(4) a magnet to apply a magnetic field to said magnetic fluid thereby to move the magnetic fluid.

5. The microreactor according to Claim 4, wherein the conduit intersects another conduit or a chamber different from the one mentioned above, so that at least two types of liquids to be transported can be mixed at the intersection.

6. The microreactor according to Claim 5, wherein said at least two types of liquids to be transported, are moved by the magnetic fluid moved solely by applying a magnetic field.

7. A method for transporting a liquid, which is a method for transporting a specific amount of an optional liquid, using a conduit wherein at least three microchannels intersect one another, and at least two of them have openings which can be opened or closed, wherein opening and closing of the openings and transportation of the liquid are carried out in a controlled order, so that a specific amount from the liquid introduced in an unspecified amount is transported.

8. The method for transporting a liquid according to Claim 7, which is a method for transporting a specific amount of an optional liquid, using a conduit wherein i) first, second and third microchannels intersect one another at one intersection, ii) the first and third microchannels have first and third openings, respectively, which can be opened or closed, iii) the intersection and the second microchannel have a portion having a specific volume, which regulates the amount of the liquid filled therein, wherein a specific amount of a liquid is transported by performing a process comprising the following steps:

(1) opening the first opening, and closing the third opening,
(2) introducing an optional liquid into the first microchannel, and transporting the liquid until its front fills the specific volume portion,
(3) closing the first opening, and opening the third opening, and
(4) transporting the liquid filled in the specific volume portion of the second microchannel to the third microchannel.

9. The method for transporting a liquid according to Claim 7, which is a method for transporting a specific amount of an optional liquid, using a conduit wherein, i) first, second and third microchannels intersect one another at a first intersection, and the second microchannel, a fourth microchannel and a fifth microchannel intersect one another at a second intersection, ii) the first, third, fourth and fifth microchannels have first, third, fourth and fifth openings, respectively, which can be opened or closed, iii) the first intersection, the second intersection and the second microchannel have a portion having a specific volume, which regulates the amount of the liquid filled therein, whereby a specific amount of a liquid is transported by performing a process comprising the following steps:

(1) opening the first and fifth openings, and closing the third and fourth openings,
(2) introducing an optional liquid into the first microchannel, and transporting the liquid so that the specific volume portion is filled with the liquid,
(3) closing the first and fifth openings, and opening the third and fourth openings, and
(4) transporting the liquid filled in the specific volume portion to the third microchannel.

10. The method for transporting a liquid according to any one of Claims 7 to 9, wherein the transportation of the liquid is performed by controlling the pressure of a gas or a liquid filled in the microchannels.

11. The method for transporting a liquid according to Claim 10, wherein the pressure control of the gas or the liquid is performed by introducing a magnetic fluid in the microchannels, and applying a magnetic field to the magnetic fluid.

Fig. 1

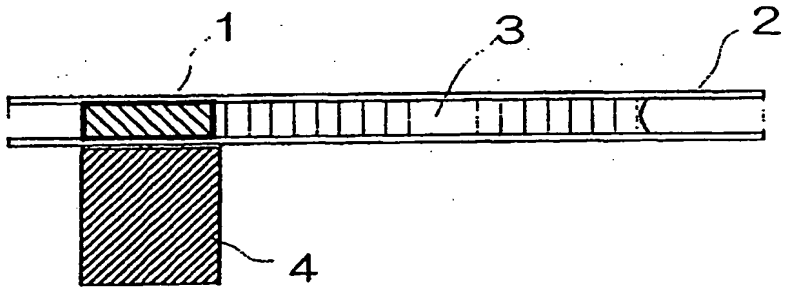


Fig. 2

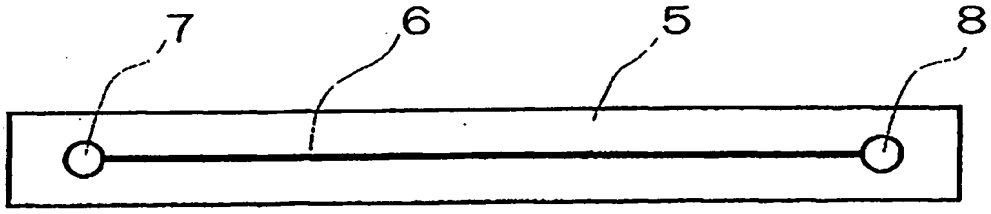


Fig. 3

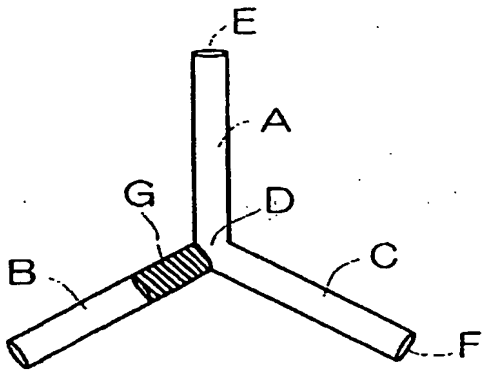
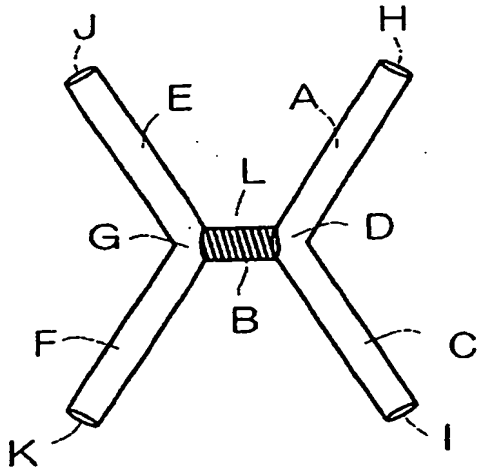


Fig. 4



Status of openings					
Opening 16	Opening 17	Opening 18	Opening 19	Opening 20	
Open	Open	Open	Open	Open	
Open	Open	Open	Open	Open	
Open	Open	Open	Open	Close	
Close	Close	Open	Open	Open	
Close	Close	Open	Open	Open	

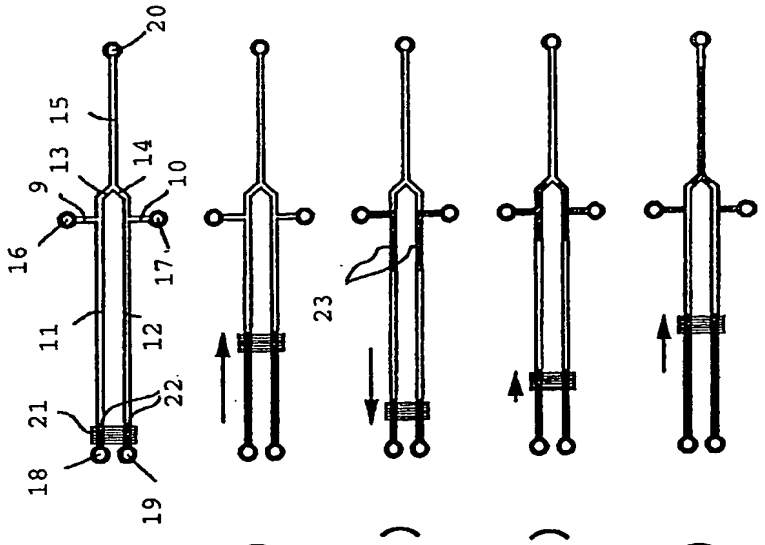


Fig.5 (i)

Fig.5 (ii)

Fig.5 (iii)

Fig.5 (iv)

Fig.5 (v)